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IP

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.

EXAMINER

ART UNIT	PAPER NUMBER
	33

DATE MAILED:

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No.	Applicant(s)
08/366,083	Pomerantz et al.
Examiner	**Group Art Unit**
Terry A. McKelvey	1636

X Responsive to communication filed on 7/5/0

This action is **FINAL**.

Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte* Quayle, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *three* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

X Claim(s) *1-21, 24, 27-30, 34, 36, 40-70, and 72-98* is/are pending in the application.

Of the above, claim(s) *1-21, 24, 27-30, 34, and 36* is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

X Claim(s) *40-70 and 72-98* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____.

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☐ Notice of References Cited, PTO-892

☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

-- SEE OFFICE ACTION ON THE FOLLOWING PAGES --

DETAILED ACTION

Continued Prosecution Application

The request filed on 7/5/00 for a Continued Prosecution Application (CPA) under 37 CFR 1.53 d based on parent Application No. 08/366,083 is acceptable and a CPA has been established. An action on the CPA follows.

Election/Restriction

Claims 1-21, 24, 27-30, 34, and 36 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b) as being drawn to a non-elected invention. Election was made **without** traverse in Paper No. 12.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 40-70 and 72-98 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not

described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a new rejection.

The claimed invention is drawn to a nucleic acid and its use, the nucleic acid encoding a chimeric protein which binds a nucleic acid comprising a composite binding site, wherein the chimeric protein comprises two nucleic acid binding domains, each of which binds a sequence which is a portion of the composite binding site, and wherein the two nucleic acid binding domains do not occur in the same protein in nature, do not occur in the same protein in nature in the order in which they are present in the chimeric protein, or do not occur in nature with the same spacing that is present in the chimeric protein.

These are genus claims. The specification fails to disclose even one embodiment that definitively meets the claim limitations because the specification does not teach that any one embodiment is definitely not present in nature. The specification also fails to teach how one of skill in the art would know that a particular combination of nucleic acid binding domains are definitely not found encoded in a natural gene. There is no description of what combinations of nucleic acid binding domains

definitely do not exist in nature. The general knowledge in the art concerning known genes and gene mutations does not provide any indication of the excluded structures of nucleic acids of natural genes that have not been identified or sequenced yet, but which are still excluded by the claim limitations. The nature of different genes in the art is that they tend to vary unpredictably and thus, unless the nucleotide sequence of the different genes are empirically determined, they are not known and not predictable. The present and foreseeable state of the art is that the structure of one or more known genes does not predict the specific structures of one or more other genes that are presently unknown. The common structural attributes of the genus are not described. One of skill in the art would conclude that applicant was not in possession of the claimed genus, especially because there is no description of even one member of the claimed genus that definitively meets the claim limitations because it was not shown that the nucleic acid was not present in nature, and thus, the description of the claimed invention is insufficient to support the claims.

Claims 40-70 and 72-98 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not

described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. This is a new rejection.

The claimed invention is drawn to a nucleic acid and its use, the nucleic acid encoding a chimeric protein which binds a nucleic acid comprising a composite binding site, wherein the chimeric protein comprises two nucleic acid binding domains, each of which binds a sequence which is a portion of the composite binding site, and wherein the two nucleic acid binding domains do not occur in the same protein in nature, do not occur in the same protein in nature in the order in which they are present in the chimeric protein, or do not occur in nature with the same spacing that is present in the chimeric protein.

Enablement is considered in view of the *Wands* factors (MPEP 2164.01(a)). These include: nature of the invention, the state of the prior art, the predictability or lack thereof in the art, the amount of direction or guidance present, the presence or absence of working examples, the quantity of experimentation necessary, the relative skill levels of those in the art, and the breadth of the claim. The most relevant Wands factors for

evaluating the enablement of the instant rejection are discussed below.

The nature of the invention is complex because the exclusion conditions that form a limitation of the claimed nucleic acids and methods is complex, that such a combination of nucleic acid binding domains is not present in nature, nature being hugely complex. There are a limitless number of genes encoding different proteins in nature, especially including natural recombinants of those genes which resulted from a fusion between genes encoding different proteins, including different DNA binding proteins, which may result in natural chimeric nucleic acids as claimed (excluding the not present in nature part of the claim limitations). An example of such natural fusions that occurs in nature are chromosomal breakpoint mutations, some of which involve DNA binding proteins.

The nucleic acids which meet the claimed limitations are highly unpredictable because for any given nucleic acid, all of the natural nucleic acids that exist in the natural world must be empirically determined and their sequences searched in order to determine whether the particular nucleic acid is encompassed by the claims or not. Without doing this, it is impossible to predict for any given combination of nucleic acid binding domains

in a chimeric protein encoded by a nucleic acid, whether the nucleic acid meets all of the claim limitations, including the exclusions.

The amount of guidance is slight because both the art and the specification fail to teach even a small fraction of all possible sequences that any given nucleic acid must be compared to in order to determine whether that nucleic acid exists in nature or not.

Neither the art nor the specification teaches a working example of the claimed invention because neither the art nor the specification teaches a nucleic acid that definitively meets the claim limitations, that the combination of nucleic acid binding domains does not exist in nature.

In order to practice the claimed invention, one skilled in the art would have to envision an embodiment of the claimed invention, make it, test it in order to see whether it is functional in binding a composite DNA binding site, and if it does, then one skilled in the art would have to determine the nucleotide sequence of all genes that exist in nature, including mutant genes, and then compare the functional nucleic acid with all natural gene sequences in order to determine whether or not the nucleic acid is present in nature or not, and if it is not

present in nature, then it is one functional embodiment that meets the claim limitations, out of the broad scope as claimed. This would require an absolutely enormous amount of experimentation because the nucleotide sequences of all natural genes, including all natural gene mutations would have to be determined in order to determine whether any particular nucleic acid meets the claim limitations. This amount of experimentation could not be accomplished in less than an infinite amount of time to practice even only one embodiment, which would be considered to be undue to practice the invention as broadly claimed.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered

therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

Claims 40-70, 72, 89-92, 94-95, and 97 are rejected under 35 U.S.C. 103(a) as being unpatentable over Park et al (AW2) in view of Mitchel et al (S), Harrison (T) and Schultz (U). This rejection is maintained for reasons of record set forth in Paper No. 23, mailed 11/9/98 and Paper No. 27, mailed 8/4/99, and repeated below. Applicants' arguments filed 7/5/00 have been fully considered but they are not deemed to be persuasive.

Park et al teach a general strategy for designing proteins to recognize specific DNA-binding sites: this strategy is to select segments of proteins, each of which recognizes particular DNA segments and to stitch these segments together via a short peptide with a cysteine crosslink in a way compatible with each peptide being able to bind to its own DNA segment. This technique creates a protein that recognizes the composite site (page 9094, column 1). This reference also teaches that use of

the Gly-Gly-Cys linker is not essential in the design, that the cysteine can be replaced and a continuous approximately 70 amino-acid protein that should recognize a predictable site can be made (page 9095, column 2). The design is not limited to v-Jun. Any protein or other molecule that recognizes a specific DNA sequence by binding along the major groove could be a candidate. Many such cases are now known so that we already have a collection of available partial-binding sites that could be combined to form composite target-binding sites for designing binding proteins. Of course, the segments of these proteins should be designed so that the intramolecular interactions are not so strong as to compete with binding to the DNA (pages 9095-9096). Park et al also teach that the strategy is not limited to two arms and that they could have stitched together three, four, or more arms with appropriate linkers to design proteins that would recognize DNA sequences with 15, 20, or 25 bp (page 9095, column 2).

Park et al do not teach to specifically use the DNA-binding domains from distinct families of nucleic acid binding domains, use of specific types of domains such as zinc-finger domains.

Mitchell et al teach that different DNA binding transcription factors are composed of a surprising variety of usually separable DNA binding and transcriptional activation

domains (page 372, column 2). This reference teaches zinc-finger domains, homeodomains, helix-turn-helix domains, steroid hormone receptor domains, leucine zipper domains, etc (pages 372-373). Various types of separable activation domains are also taught: acidic domains that can form an amphipathic alpha-helical structure, glutamine-rich domain, and proline-rich domain (pages 373-375).

Harrison teaches that many DNA-binding proteins recognize specific sites through small, discrete domains and that these domains can be interchanged between proteins, showing that they are independent folded units. Many different DNA-binding domains are taught, including HTH, homeodomains, different types of zinc-finger domains, steroid receptor DA binding domains, etc. Representative proteins having the domains, such as Zif268, etc are also taught and referenced (page 715).

Schultz teaches that enzymes can be created by adding or replacing entire binding or catalytic domains to generate hybrid enzymes with novel specificities. Selective fusion of nucleic acid-specific binding domains may produce sequence-specific DNA or RNA cleaving enzymes (page 431, column 1). This reference teaches that tailor-made enzymes have applications in chemistry, biology and medicine.

It would have been obvious to one of skill in the art at the time the invention was made to use the various DNA binding domains, activation domains, and cleavage domains, including heterologous ones, taught by Mitchell et al, Harrison, and Schultz in the general strategy for designing proteins to recognize specific DNA-binding sites taught by Park et al because Park et al teach that it is within the ordinary skill in the art to stitch the DNA binding domains together from any proteins that recognize a specific DNA sequence by binding along the major groove, to recognize a composite site and Mitchell et al, Harrison, and Schultz teach such domains that can be functionally separated and recombined with other domains. One would have been motivated to do so for the expected benefit of creating a protein that recognizes the composite site, thereby increasing the specificity of the chimeric protein, as taught by Park et al, and creating hybrid enzymes with novel specificities that have applications in chemistry, biology and medicine as taught by Schultz. Absent evidence to the contrary, there would have been a reasonable expectation of success that the domains taught by Mitchell et al and Harrison could be combined with each other to create a protein that recognizes a composite binding site as taught by Parks et al.

With regard to making a nucleic acid and vector comprising the nucleic acid which encodes the chimeric protein, it would have been obvious to do so because Parks et al teach that a continuous approximately 70 amino-acid protein that should recognize a predictable site can be made, instead of using a cysteine linker, and thus it would have been obvious to make a nucleic acid that encodes this protein and place the nucleic acid in a vector to express the protein, because such a way of making a mutated, recombinant protein is and was well known in the art.

With regard to the use of any specific domain or combinations of domains recited in the claims, it would have been obvious to make any of the recited combinations because the recited domains are all taught in the cited references or are and were well known in the art, and Parks et al teach that any combination of domains can be used, which would include heterologous ones.

With regard to the inclusion of an activation domain in the chimeric protein, it would have been obvious to do so because the cited references teach that the activation domain are separate from the DNA binding domains and thus can be included. One would have been motivated to do so for the expected benefit of making a

transcriptional activation protein that binds to a more specific composite site, as taught by Parks et al.

With regard to separating the domains by one or more amino acids in the chimeric protein, it would have been obvious to do so because Parks et al teach that the domains can be separated by a linker.

With regard to including an additional (third) nucleic acid binding domain, it would have been obvious because Park et al teach that more domains can be added, resulting in binding to a larger composite DNA binding site.

Response to Arguments

The applicant argues that Park et al does not provide any motivation to combine the references. The applicant argues that the excerpted Park et al sentences are taken out of context. The applicant argues what Park et al referred to were arms of dimeric DNA binding proteins, and they did not intend the general statements made in the cited reference to be given the broader interpretation reflected in the office action, citing several lines of evidence:

1. A later reference referring to the cited reference, defining the concept of "protein stitchery" (more narrowly).

2. Park et al limited themselves to proteins which bind along the major groove, when clearly there are DNA binding proteins which bind along the minor groove and indeed, homeodomains and zinc finger domains do make minor groove contacts.

These arguments are not persuasive for the following reasons. First, the later reference referring to a more narrow definition of protein stitchery is not persuasive that the Park et al general teachings are not meant to be interpreted broadly by one of ordinary skill in the art because most of the Park et al reference cited in the rejection is drawn to teaching one particular embodiment, which is making the chimeric protein from the arms of a dimer. That is what is being referred to in the second Park et al reference, because that specific embodiment is further explored in that reference. Thus, naturally the same particular embodiment would be referenced in the second publication in that fashion. This does not mean that the other broad teachings of the cited Park et al reference are to be ignored or interpreted in a way much narrower than the actual statements because it is well established that references must be considered for all of what they teach, which means that in the instant case, even though most of the reference applies to the more narrow embodiment, the teachings elsewhere in the reference that are clearly much more broadly applicable must also be

considered. It is these broader teachings, in combination with the other cited teachings that would suggest to one of ordinary skill in the art the claimed invention. The fact is that the cited teachings are specifically generic: "We propose a general strategy for designing proteins ... select segments of proteins, each of which recognizes particular DNA segments and to stitch these segments together ...". [Instant underlining added for emphasis.] If the reference had intended a more narrow interpretation to the specific embodiment described, then the much broader terms would not have been used, instead the description of stitching together dimer arms would have been used. But, that wasn't done. It is the examiner's contention that the broader language was specifically used and meant to be interpreted accordingly. In fact, in further support of the broader interpretation, the first sentence of the paragraph immediately after the cited section states: "As a starting point, we consider the gene-regulatory leucine-zipper proteins." This shows that the more narrow embodiment that is taught is the starting point for the general strategy, i.e., an example of the general principle broadly set forth in the reference. It is clearly not intended to be a teaching of the only embodiment possible for the general strategy that is taught.

With regard to the second line of evidence, this argument is not persuasive because it is and was well known in the art that

the vast majority of sequence-specific DNA-binding domains make their most important, sequence-specific contacts to the DNA in the major groove, not the minor groove. It is the first and last part of the cited sentence that is most important: "Any protein or other molecule that recognizes a specific DNA sequence ... could be a candidate". The rest of the sentence, "by binding along the major groove" merely recites what is and was well known in the art, that recognition of a specific DNA sequence occurs by binding along the major groove. It is and was well known in the art that although some DNA binding domains make some contact with the minor groove, the predominant, sequence-specific contacts are made in the major groove. It is the non-sequence specific DNA binding domains which are known in the art to bind in some cases predominately to the minor groove which are clearly excluded from the teachings of the reference because of the lack of sequence-specific binding. Such non-sequence-specific binding goes against the purpose of the reference, to design a protein for selective binding to a specific DNA sequence.

The applicant also argues that the following belies acceptance in the art of the broader conclusions from the Park et al reference: the publication of the applicant's work in Science. The response to this argument is discussed below.

The applicant argues that Park et al teaches cross-linked DNA binding domains of two proteins which normally bind DNA only

in the form of a homodimer and that this reference does not teach or suggest that a chimeric protein having a composite DNA binding domain consisting of two or more DNA binding domains from different types of DNA binding proteins, which do not normally interact with each other, would bind DNA with a higher affinity to the composite binding site than to portions of it. This argument is not persuasive because although the specific embodiment taught in detail by Park et al is a protein that is a cross-linked DNA binding domain of two proteins that normally bind as a homodimer, Park et al also generically teach the use of any DNA binding domains in forming a composite DNA binding protein and that a continuous approximately 70 amino-acid protein that should recognize a predictable site can be made, instead of using a cysteine linker (and hence such a protein can be encoded into DNA). Park et al teach selecting segments of proteins, each of which recognizes particular DNA segments and stitching these segments together and that any protein or other molecule that recognizes a specific DNA sequence could be a candidate. This reference teaches that the resulting protein recognizes the composite site (and thus it would be interpreted to one of ordinary skill in the art that it is meant that binding to the composite site occurs with higher affinity than to portions of the composite site). Park et al teaches that the design is not

limited to v-Jun. Any protein or other molecule that recognizes a specific DNA sequence by binding along the major groove could be a candidate. Many such cases are now known so that we already have a collection of available partial-binding sites that could be combined to form composite target-binding sites for designing binding proteins. These teachings clearly show that two or more DNA binding domains from different types of DNA binding proteins was generically contemplated by Park et al, and the other cited references teach the separation of DNA binding domains of various types from the other domains of DNA binding proteins.

The applicant also argues that neither of the Harrison and Mitchell et al references refer to portions of DNA binding domains, e.g. individual zinc finger domains, which can also constitute part of the applicant's claimed invention. This argument is not persuasive because the applicant is arguing a limitation that is not present in the claims, that the two parts of the chimeric protein that are responsible for binding to the final composite binding site can be "portions" of DNA binding domains. The actual limitations which the applicant appears to be referring to merely indicates that the nucleic acid binding domains (which is only properly read as whole nucleic acid binding domains) include a particular motif (open language), not that they consist of a particular motif (closed language) which

when closed only reads on a portion of a nucleic acid binding domain. The art rejections of record are not based upon the obviousness of combining portions of nucleic acid binding domains together, and in fact, such a limitation probably would overcome the art rejections.

With regard to the applicant's discussion of the basis of the reasonable expectation of success, it was previously discussed in detail. The combined teachings of the cited references provides the reasonable expectation of success, not the Harrison or Mitchell references by themselves. The main source is the Park et al reference which shows that a chimeric protein can be made by fusing together two nucleic acid binding domains that separately binds to half of the composite site recognized by the fusion, resulting in a protein that binds to the composite site (which of course, by preferentially binding to the composite site, does so at a higher affinity than binding to either of the original individual sites). The Harrison and Mitchell references show that there would have been a reasonable expectation of success of obtaining the nucleic acid binding domains as discrete domains for use in the general strategy taught by Park et al. The applicant also questions the reasonable expectation of success that binding of the chimeric protein containing a transcriptional activation domain to a DNA binding site would be able to stimulate transcription of a target

gene. This argument is not persuasive because it is and was well known in the art that transcriptional activation could be achieved by linking the transcriptional activation domain to a heterologous DNA binding domain in order to achieve DNA binding site dependent transactivation; this was taught by Gossen et al, which reference provides reasonable expectation of success for achieving such activation in an analogous chimeric protein made from the combined teachings of the cited references.

The applicant also argues that the statement by the inventor of the instant application after publication in Science, "laboratory tests have proved the artificial switch can find, and control, a single gene among the 80,000 that exists in humans.", and another author's quote "the critical thing was showing it can find the proper site.", and that if there had been a reasonable expectation of success, the paper couldn't have been published. These arguments are not persuasive because "reasonable expectation of success" is a legal standard which is not the same as the standard applied to determination of whether something is or is not to be published. Publication is based upon other factors and novelty in the art, which is not argued by the examiner as shown by the lack of a rejection under 35 USC 102, not whether or not other references in the art in combination suggest the claimed invention, as per the Graham v. Deere analysis of obviousness. This also applies to the cited comments

which essentially discuss whether the novel findings that were published actually operate. These comments have no bearing on whether the particular combination of teachings of the cited reference legally make obvious the claimed invention and provide a reasonable expectation of success.

The applicant also argues that although Park et al teach that a peptide bond can link the two DNA binding domains, a person of skill in the art would have known that a peptidic bond may give rise to a protein structure that is different from that resulting from disulfide cross-linking and thus there is no reasonable expectation of success. This argument is not persuasive because the Park et al reference specifically states that the linker is not essential in the design, and that they could just as well replace the cysteine and make a continuous protein that should recognize a predictable site. From the cited teachings it would have been expected that some embodiments would function and be successful and some would not, and that simple and routine testing of different possible embodiments would identify those that function and those that fail to function. Thus, there would have been a reasonable expectation that some embodiments would function and that it would have been expected that the functional ones could be easily identified. This teaching and the rest of the references provides the reasonable expectation of success. One of ordinary skill in the art would

apply the relevant teachings of the cited art to make a single protein that had the specific peptide bonds which result in the functional chimeric protein.

Therefore in light of the rejection set forth above and in the previous Office Action, the applicant's arguments, and the arguments set forth above, the claimed invention is still considered to have been obvious and the rejection under 35 USC 103(a) is maintained.

Claims 40-70 and 72-98 are rejected under 35 U.S.C. 103(a) as being unpatentable over Park et al (AW2), Mitchel et al (S), Harrison (T) and Schultz (U) as applied to claims 40-72 above, and further in view of Gossen et al (A). This rejection is maintained for reasons of record set forth in Paper No. 23, mailed 11/9/98 and Paper No. 27, mailed 8/4/99, and repeated below. Applicants' arguments filed 7/5/00 have been fully considered but they are not deemed to be persuasive.

The teachings of Park et al (AW2 , Mitchel et al (S), Harrison (T) and Schultz (U) are cited above and applied as before. These references do not specifically teach placing the nucleic acid encoding the chimeric protein into a vector in which the expression of the chimeric protein is under the control of a promoter permitting gene expression in eukaryotic cells, a kit

comprising the nucleic acid encoding the chimeric protein and a gene operably linked to the composite binding site, use of the chimeric protein for modulating expression of a gene in a cell comprising modulating expression of the chimeric protein in a cell which includes a gene operably linked to the composite binding site, and a method of making a cell for use in the claimed expression method.

Gossen et al teach a nucleotide molecule coding for a chimeric transactivator fusion protein comprising a DNA binding domain (tet repressor binding domain) and a transactivation domain (such as VP16 of HSV). A negative system, comprising a repressor domain, is also taught (column 2). A second nucleic acid is taught coding for a heterologous protein which is operably linked to a tet operator (the binding site for the DNA binding domain). A method to regulate gene expression by cultivating the eukaryotic cell comprising the nucleic acid vectors in a medium comprising tet is also taught, as is a kit comprising the nucleic acids (abstract; columns 1-3). A method of making such eukaryotic cells by transfecting the nucleic acids into the cells is taught (columns 3, 9). This reference also teaches that it is desired to create regulatory systems that do not rely on endogenous control elements (column 1).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to form a transcriptional regulatory system from the DNA encoding a chimeric transactivation protein made obvious by the teachings of Park et al (AW2), Mitchel et al (S), Harrison (T) and Schultz (U), using the method taught by Gossen et al because Gossen et al teach that it is within the ordinary skill in the art to make a nucleic acid vector that encodes a chimeric transactivator fusion protein (under the control of a promoter active in eukaryotic cells), make a nucleic acid encoding a heterologous protein operably linked to a regulator binding site that the chimeric protein binds to, place the nucleic acids in a eukaryotic cell, regulate the expression of the chimeric protein, thereby regulating expression of the heterologous protein, and the other cited references teach a chimeric fusion transactivator protein that could be used to regulate the expression of genes in a similar fashion as that taught by Gossen et al. One would have been motivated to do so for the expected benefit of making regulatory systems that do not rely on endogenous control elements, the desirability of which is taught by Gossen et al. Absent evidence to the contrary, there would have been a reasonable expectation of success that the chimeric protein encoding DNA taught by the

other cited references could be used to make a new, non-endogenous element regulatory system using the teachings of Gossen et al.

Response to Arguments

With regard to the instant rejection, the applicant essentially repeated the arguments set forth in the previous rejection above and stated that the Gossen reference does not cure the alleged defects in the rejection. Gossen et al was not relied upon for those teachings, but instead was used to show the obviousness of claims with additional limitations. The applicant did not argue those additional limitations. The applicant's arguments with regard to the alleged defects were addressed above and are equally applicable in the instant rejection. Therefore, the applicant's arguments have already been fully addressed and thus the instant rejection under 35 USC 103(a) is maintained for the same reasons as the rejection set forth above.

Conclusion

No claims are allowed.

Certain papers related to this application may be submitted to Art Unit 1636 by facsimile transmission. The faxing of such papers must conform with the notices published in the Official

Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 C.F.R. § 1.6(d)). The official fax telephone numbers for the Group are (703) 308-4242 and (703) 305-3014. NOTE: If Applicant *does* submit a paper by fax, the original signed copy should be retained by applicant or applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED so as to avoid the processing of duplicate papers in the Office.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Terry A. McKelvey whose telephone number is (703) 305-7213. The examiner can normally be reached on Monday through Friday, except for Wednesdays, from about 6:30 AM to about 5:00 PM. A phone message left at this number will be responded to as soon as possible (usually no later than 24 hours after receipt by the examiner).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. George Elliott, can be reached on (703) 308-4003.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Terry A. McKelvey

Terry A. McKelvey, Ph.D.
Primary Examiner
Art Unit 1636

September 20, 2000